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The Bottom Line

Improved Survival after Cord Blood Transplantation: Single-Center Experience in Pediatric Patients Over a 2-Decade Period



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Umbilical cord blood transplantation (UCBT) is an alternative hematopoietic stem cell source for patients with hematologic diseases who can be cured by allogeneic hematopoietic cell transplantation [1]. The results for UCBT have improved with an increased emphasis on the use of cord blood (CB) units of sufficient cell dose, sufficient HLA matching, use of double CB units, and improved supportive care techniques [2].

In this issue of the *Journal*, Spees et al. [3] report on 824 pediatric patients who underwent UCBT in 3 periods: 1995 to 2001, 2002 to 2007, and 2008 to 2014. Several points in the study are of interest. First, the indications for UCBT have changed over time, with decreased use in patients with hematologic malignancies and increased use in patients with nonmalignant disorders. Second, the shift to increased use of UCBT in patients with nonmalignant disorders has occurred concomitantly with other practice changes, including the more frequent use of double-unit UCBT, use of reduced-intensity conditioning regimens, improvements in supportive care, and use of a calcineurin inhibitor plus mycophenolate for GVHD prophylaxis.

Spees et al. do not provide a specific analysis of effect of allele HLA-matching on UCBT outcomes. The risk of death was higher in black and other minority children compared with white children. Interestingly, white children were more likely to receive better HLA-matched and race-matched CB units than black and other minority children. Several previous studies have shown better outcomes in patients receiving single-unit UCBT using better HLA allele-matched CB units [4]. The results of this study support the importance of increasing the collection of CB units from racial minorities; however, the decrease in the number of UCBTs performed annually has been accompanied by a significant reduction in the number of public

CB banks. The recent closure (2018) of the St. Louis public CB bank raises the concern that this situation may disproportionately affect areas with larger minority populations.

Spees et al. identify a reduction in infectious mortality as the greatest contributor to this improved survival after UCBT. The delayed immune reconstitution in recipients of CB grafts is well established [5]. The impaired functional recovery of a graft that is naive and thus more permissive to viral reactivation and uncontrolled viral replication puts UCBT recipients at particularly high risk for viral reactivation and disease [6]. Cytomegalovirus (CMV) and adenovirus (AdV) are of particular concern in these patients. Retrospective studies from the late 1990s to early 2000s reported an incidence of CMV reactivation ranging from 21% to 100%, with CMV disease occurring in 6% to 21% of patients [7]. These data preceded the implementation of interventions aimed at decreasing CMV reactivation and disease. Although Spees et al. state that antiviral medications, such as ganciclovir and foscarnet, have not been proven effective in CMV prevention, we have shown decreased viral reactivation and, importantly, CMV disease in patients treated with an intensive prophylactic approach before transplantation [7]. These medications do have significant toxicities, however, and so more recently we have modified our preventive approach in adult patients [8] with plans to extend these modifications to the pediatric population. Newer antiviral medications, such as letermovir, appear promising and may further change the clinical approach to CMV prophylaxis [9]. Viral-specific cytotoxic T lymphocytes (CTLs) are another novel approach to treatment of CMV, AdV, and other viral infections [10]. These therapies were originally donor-derived products and thus were not available to UCBT recipients; however, in more recent studies investigating the use of third-party donors, partially matched CTLs have shown particular promise for UCBT recipients [10]. We hope that with newer antiviral medications and cellular therapies, further improvement in viral infections will be seen over the next 5 to 6 years, especially for AdV. Spees et al. note significant improvement in invasive fungal infections as well, a trend that has been observed in recipients of allogeneic transplants [11] and is certainly holds promise for reductions in infectious morbidity and mortality.

Spees et al. provide an excellent overview of changes in UCBT over 2 decades and identify future areas of focus for the

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UCBT community. A major focus should be on collection of CB units from areas serving minority populations to provide a more diverse donor pool. In addition, ongoing efforts to decrease infections are important, with a focus on new antiviral medications and third-party cellular therapies. Finally, standardizing infection prevention approaches across UCBT centers may help further decrease mortality going forward.

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